Seizure 20 (2011) 160–162

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Pilot association study of oxcarbazepine-induced mild cutaneous adverse reactions with HLA-B*1502 allele in Chinese Han population

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ARTICLE INFO

Article history:
Received 14 June 2010
Received in revised form 26 October 2010
Accepted 22 November 2010

Keywords:
Antiepileptic drugs
Oxcarbazepine
HLA-B*1502
Maculopapular eruption
Cutaneous adverse drug reactions

ABSTRACT

Background: Recent study demonstrated that HLA-B*1502 was a common risk allele in aromatic antiepileptic drugs (AEDs) induced Stevens–Johnson syndrome and toxic epidermal necrolysis in Han Chinese. However, the association of AEDs-induced mild maculopapular eruption (MPE) with HLA-B*1502 remains unclear until recently. In the present study, we conducted a pilot study to detect a possible association of oxcarbazepine (OXC)-induced MPE with HLA-B*1502 allele in Chinese Han population.

Methods: We enrolled 90 subjects involving 9 patients with OXC-induced MPE and two groups of controls, 9 OXC-tolerant and 72 normal controls. High-resolution HLA genotyping was performed by specific kit. The results of HLA genotyping are expressed as positive or negative for HLA-B*1502 allele. Differences in genotype frequencies between groups were assessed by the Fisher's exact test.

Results: Four cases were detected as positive for HLA-B*1502 amongst 9 patients. However, only 1 subject was positive amongst 9 tolerant controls, and 6 subjects were positive amongst 72 normal controls. The difference in HLA-B*1502 allele frequencies between the MPE group and normal controls was statistically significant (OR: 8.8; 95% CI: 1.853–41.790; $P = 0.011$). In addition, we also observed an increased frequency of HLA-B*1502 allele in patients (44.44%) compared with tolerant controls (11.11%), although it failed to reach statistical significance ($P = 0.294$).

Conclusions: Our findings indicate that HLA-B*1502 allele may contribute to the genetic susceptibility to OXC-induced MPE in Chinese Han population. In order to safer AEDs use, we recommend that HLA-B*1502 allele should be tested for patients with OXC-induced MPE before changing to other AEDs, and AEDs with similar chemical structure should be avoided in individuals who test positive for HLA-B*1502 allele. It should be pointed out that, however, our results may well be just by chance owing to the small sample size and should be further confirmed in future studies.

1. Introduction

Antiepileptic drugs (AEDs) are one of the most common causes of cutaneous adverse drug reactions (cADRs). cADRs are mostly unpredictable and potentially life-threatening during antiepileptic therapy. The clinical manifestation of cADRs varies from mild maculopapular eruption (MPE), with increasing severity, to life-threatening severe cutaneous reaction (SCR), which includes Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug hypersensitivity syndrome (HSS).[1] The overall incidence of various forms of AEDs-induced cADRs is approximately 10%.[2] MPE is more common than HSS or SJS/TEN with an overall incidence rate of 2.8% amongst all AEDs users.[3] cADRs is a large burden on healthcare system and antiepileptic therapy is often limited by different cADRs. Therefore, preventing these cADRs is an important goal for improving patient safety.

Recent pharmacogenetic studies have uncovered a strong association between carbamazepine (CBZ)-induced SJS/TEN and human leucocyte antigen HLA-B*1502 allele in Asian populations.[4–9] These data indicate that HLA-B*1502 allele may be a genetic marker for CBZ-induced SJS/TEN in Asians other than Han Chinese. Identification of genetic factors contributing to the development of AEDs-induced SCR offers the possibility of avoiding these high-risk drugs in genetically susceptible individuals. Therefore, the United States Food and Drug Administration (US FDA) updated the CBZ label to include genetic information and recommended genetic screening for HLA-B*1502 allele before starting CBZ therapy in Asians.[10] These genetic advances arose increasing scientific interest amongst researchers to examine the

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doi:10.1016/j.seizure.2010.11.014

other aromatic AEDs with a similar structure to CBZ, such as lamotrigine and OXC. Further study demonstrated that aromatic AEDs-induced SJS/TEN share a common risk allele HLA-B*1502.[9]

Here, an important issue has been arose whether AEDs-induced MPE is associated with HLA-B*1502 allele. Previous pharmacogenetic studies focused primarily on the AEDs-induced SCR. Regretfully, AEDs-induced MPE has attracted less attentions, although it may also be important to reveal the genetic link of AEDs-induced cADRs. Recent study suggested that CBZ-induced MPE was lack of association with HLA-B*1502 allele.[5] However, the association between other AEDs-induced MPE and HLA-B*1502 allele has not been examined in different ethnic populations. In the present study, we conducted a pilot study to detect a possible association of OXC-induced MPE with HLA-B*1502 allele in Chinese Han population from mainland China.

2. Patients and methods

The study protocol was approved by the Ethics committee of Sichuan University and written informed consent was obtained from all participants. We conducted a case–control association study involving 9 patients with OXC-induced MPE and two groups of controls, 9 OXC-tolerant and 72 unrelated healthy controls. All patients with OXC-induced MPE were consecutively recruited from our epilepsy center. In addition, we enrolled 9 subjects who had been on OXC for more than 3 months without any cADRs as tolerant controls. All cases and controls were ethnic Han Chinese indigenous to mainland China. MPE is characterized by cutaneous itchy and erythematous macules and papules after administration of antiepileptic medicines, and spontaneously resolve within 1–2 weeks after withdrawing the causative drugs.[11] Genomic DNA was extracted from peripheral blood lymphocytes using standard phenol–chloroform procedures. High-resolution HLA genotyping was performed by polymerase chain reaction sequencing-based typing (PCR-SBT) assay using specific kit (Bioassay Laboratory of CapitalBio Corporation, Beijing, China). The results of HLA genotyping are denoted as positive or negative for HLA-B*1502 allele. Fisher's exact test was used to analyze the possible association between OXC-induced MPE and HLA-B*1502 allele. A two-tailed P value of <0.05 was considered to be statistically significant.

3. Results

In this study, we successfully performed high-resolution HLA genotyping for 90 subjects. Four cases were demonstrated as positive for HLA-B*1502 allele amongst 9 patients with OXC-induced MPE. By comparison, only 1 subject was positive for HLA-B*1502 allele amongst 9 OXC-tolerant controls, and 6 subjects were positive amongst 72 normal controls (shown in Table 1). The difference in HLA-B*1502 frequency between the MPE group and normal controls was statistically significant (OR: 8.8; 95% CI: 1.853–41.790; $P = 0.011$). In addition, we also found that patients with OXC-induced MPE (44.44%) had an increased frequency of the HLA-B*1502 allele compared with OXC-tolerant controls (11.11%), although it failed to reach statistical significance ($P = 0.294$).

Table 1
Allele frequencies of HLA-B*1502 amongst all subjects.

Groups	N	Allele (%)	
		HLA-B*1502	Non HLA-B*1502
OXC-induced MPE[a]	9	4 (44.4%)	5 (55.6%)
OXC-tolerant control	9	1 (11.1%)	8 (88.9%)
Normal control[b]	72	6 (8.3%)	66 (91.7%)

[a] OXC-induced MPE compared with OXC-tolerant control: odds ratio = 6.4, 95% CI: 0.5471–74.891, $P = 0.294$.
[b] OXC-induced MPE compared with normal control: odds ratio = 8.8, 95% CI: 1.853–41.790, $P = 0.011$.

Clinical characteristics of the 9 patients with OXC-induced MPE are summarized in Table 2. The onset of symptoms for all patients with MPE occurred within the first 40 days of OXC exposure. Amongst these patients, including four males and five females, the mean dosage of OXC was 366.7 mg/day and latency to MPE from drug exposure was 17.3 days. For the four HLA-B*1502 allele carriers, the mean dosage of OXC was 300 mg/day and the latency to MPE was 14.5 days. All patients with OXC-induced MPE were complete recovery after withdrawing the causative drugs. By comparison, the tolerant controls received OXC with a mean dosage of 533.3 mg/days and duration of more than 3 months. It can be seen that the tolerant controls administrated higher doses of OXC than the MPE groups and no adverse drug reactions were observed.

4. Discussion

A new anticonvulsant, OXC, was introduced into Chinese market for antiepileptic therapy before 7 years. OXC, a 10-keto analogue of CBZ, is considered to be much safer than CBZ owing to its different metabolic pathway.[12] OXC is almost completely metabolized through reduction and conjugation to yield an active monohydroxy derivative (MHD), which is glucuronidated and excreted in the urine. In contrast, the oxidation of CBZ to 10,11-epoxide is regarded as the most common cause of side effects.[13] The estimated relative risk of OXC-SJS was 30–40-fold lower than that of CBZ-SJS in Han Chinese of Taiwan.[14] To date, only five patients with OXC-induced SJS/TEN have been reported, and four of them were HLA-B*1502 positive.[9,14,15] Recently, OXC is increasingly used as first-line drug in the treatment of partial epilepsy with or without secondary generalization in mainland China due to the better safety than CBZ. Although OXC and CBZ share the similar chemical structure, significant differences still exist in all aspects between the two drugs.[13] Therefore, it is necessary to further examine the possible association of OXC-

Table 2
Characteristics of patients with oxcarbazepine-induced MPE.

Patient ID	Sex	Age (years)	Race	Disease	Dose of OXC (mg)	Latency to MPE (days)	HLA-B*1502 allele
1	F	14	Han Chinese	Epilepsy	300	14	Positive
2	M	22	Han Chinese	Epilepsy	600	16	Negative
3	M	8	Han Chinese	Epilepsy	300	10	Negative
4	M	16	Han Chinese	PKC	300	2	Negative
5	F	17	Han Chinese	Epilepsy	300	40	Negative
6	M	16	Han Chinese	Epilepsy	150	21	Positive
7	F	18	Han Chinese	Epilepsy	600	30	Negative
8	F	29	Han Chinese	Epilepsy	300	5	Positive
9	F	16	Han Chinese	Epilepsy	450	18	Positive

PKC: paroxysmal kinesigenic choreoathetosis; MPE: maculopapular eruption.

induced MPE and HLA-B*1502 allele, although prior study failed to show significant association between CBZ-induced MPE and HLA-B*1502 allele.[5]

The present study demonstrated an association between HLA-B*1502 allele and OXC-induced MPE in Han Chinese. The risk of OXC-induced MPE was significantly higher in the patients with the HLA-B*1502 allele, with an OR of 8.8 (95% CI: 1.853–41.790, $P = 0.011$). Furthermore, we also observed a higher frequency of HLA-B*1502 allele in patients with OXC-induced MPE compared to OXC-tolerant controls. Therefore, we speculate that HLA-B*1502 allele may increase the genetic risk for OXC-induced MPE in Chinese Han population. Our results are different from those of the previous study, suggesting that there was no significant association of CBZ-induced MPE with HLA-B*1502 allele.[5] These discrepant results could be mainly due to different chemical structure between OXC and CBZ. In addition, other HLA alleles or genetic markers/environmental factors may also contribute to the development of AEDs-induced MPE, except for HLA-B*1502 allele. Previous study have found that CBZ-induced MPE was associated with some single nucleotide polymorphisms (SNPs, including rs1264511 and rs1059510) in the HLA-E region and a nearby allele, HLA-A*3101.[5]

Patients who develop cADRs on one drug may develop another episode of cADRs when changed to other drugs with similar chemical structures.[16] This crossreactivity has been observed in patients receiving antiepileptic medicines. Furthermore, cADRs are most commonly encountered amongst patients treated with aromatic AEDs.[17,18] Previous clinical studies indicated that aromatic AEDs, including CBZ, OXC, Phenobarbital (PB), phenytoin (PHT) and lamotrigine (LTG), have a 20–30% chance of cross-reacting, and 25–70% of OXC-hypersensitive patients react to CBZ.[19–21] Recent retrospective observation in Chinese population showed that 66.7% of OXC-hypersensitive patients react to CBZ, 25% of OXC-hypersensitive patients react to LTG and 25% of OXC-hypersensitive patients react to PHT.[22] Although these cross-reactivities of cADRs are primarily observed as mild skin rashes, such as MPE.[11] However, it remains unclear whether patients with OXC-induced MPE will develop another episode of MPE or SCR when changed to other AEDs. Therefore, caution is necessary when prescribing the alternative AEDs for patients with OXC-induced MPE. Given the high frequency of HLA-B*1502 allele in patients with OXC-induced MPE and the crossreactivities of cADRs amongst various AEDs, we recommend that HLA-B*1502 allele should be tested for patients with OXC-induced MPE before changing to other AEDs, and that other aromatic AEDs should be avoided in individuals who develop OXC-induced MPE and simultaneously test positive for HLA-B*1502 allele.

In this exploratory study, we specifically typed the HLA-B gene to detect the presence of HLA-B*1502 allele using a commercial kit. This kit is based on the sequencing assay and thus has good specificity. To our knowledge, this is the first report that show an association between AEDs-induced MPE and HLA-B*1502 allele in Chinese Han population. Therefore, our results may have a positive effect on the genetic study of AEDs-induced cADRs and safe AEDs use in future, although it may be not sufficient to influence the present clinical practice. However, it should be noted that this is a small sample study, which limited the statistical power to detect a significant difference in HLA-B*1502 allele frequency between cases and controls. Therefore, our results may be just a chance finding and need to be further confirmed in larger studies.

Acknowledgements

This study was supported by Program for Changjiang Scholars and Innovative Research Team in University of China (No. IRT0847). We would like to thank all subjects who took part in this study.

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